Intraindividual Increase of Homeostatic Sleep Pressure Across Acute and Chronic Sleep Loss: A High-Density EEG Study

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Intra-individual increase of homeostatic sleep pressure across acute and chronic sleep loss: A high-density EEG study.

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ABSTRACT

Study Objectives: To compare intra-individually the effects of acute sleep deprivation (ASD) and chronic sleep restriction (CSR) on the homeostatic increase in slow wave activity (SWA) and to relate it to impairments in basic cognitive functioning, i.e. vigilance.

Methods: The increase in SWA after ASD (40 hours of wakefulness) and after CSR (7 nights with time in bed restricted to 5 hours per night) relative to baseline sleep was assessed in 9 healthy, male subjects (age = 18-26 y) by high-density electroencephalography (EEG). The SWA increase during the initial part of sleep was compared between the two conditions of sleep loss. The increase in SWA was related to the increase in lapses of vigilance in the psychomotor vigilance task (PVT) during the preceding days.

Results: While ASD induced a stronger increase in initial SWA than CSR, the increase was globally correlated across the two conditions in most electrodes. The increase in initial SWA was positively associated with the increase in PVT lapses.

Conclusions: The individual homeostatic response in SWA is globally preserved across acute and chronic sleep loss, i.e. individuals showing a larger increase after ASD also do so after CSR and vice versa. Furthermore, the increase in SWA is globally correlated to vigilance impairments after sleep loss over both conditions. Thus, the increase in SWA might therefore provide a physiological marker for individual differences in performance impairments after sleep loss.

Keywords: sleep deprivation, sleep restriction, slow wave activity, sleep homeostasis, vigilance

STATEMENT OF SIGNIFICANCE

Chronic sleep loss is highly prevalent in modern society. Individuals differ considerably in the extent of performance impairment after sleep loss, and these differences persist across acute and chronic sleep loss. Distinct characteristics in sleep regulatory mechanisms are likely contributing to these differences. An increase in electroencephalography (EEG) slow wave activity (SWA) during initial sleep

is a reliable electrophysiological marker of increased sleep pressure. Here we show that individual differences in the increase of SWA are preserved across acute and chronic sleep loss. Furthermore, the increase was found to relate to impairments in vigilance. Thus, the increase in SWA might be a potential marker for individual differences in performance impairments after sleep loss.

ABBREVIATIONS

AIC	Akaike information criterion
ASD	Acute sleep deprivation
BIC	Bayesian information criterion
BL	Baseline
CSR	Chronic sleep restriction
EEG	Electroencephalography
NREM(S)	Non-rapid eye movement (sleep)
PVT	Psychomotor vigilance task
SnPM	Statistical non-parametric mapping
REM(S)	Rapid eye movement (sleep)
SWA	Slow wave activity
WASO	Wake after sleep onset

INTRODUCTION

It is well-known that acute sleep deprivation (ASD), i.e. a one-time prolongation of wakefulness, negatively impacts a variety of cognitive functions.[1,2] While strong effects are consistently found for simple attention and vigilance tasks on a group-level,[2] large inter-individual differences exist in the extent of these effects. In fact, these differences range from almost resistant to highly vulnerable subjects and persist within subjects across repeated exposure to ASD (e.g.,[3]). Recently an increasing body of research focuses on the effects of chronic sleep restriction (CSR), a condition of repeated partial sleep loss. The major reason for the growing interest in CSR is that it resembles everyday sleep loss much more than ASD, as more individuals in our society suffer from chronically inadequate sleep durations than from ASD.[4-6] CSR, depending on the duration and extent of sleep restriction, has been shown to lead to comparable impairments in vigilance, working memory and cognitive throughput as ASD.[7] Interestingly, across both ASD and CSR, an individual's vulnerability to develop impairments following sleep loss persists.[8]

On the electrophysiological level, slow wave activity (SWA) during non-rapid eye movement (NREM) sleep, i.e., the EEG spectral power between 0.5-4.5 Hz,[9] is an established marker of increased sleep pressure due to prolonged wakefulness. More specifically, we know from numerous ASD studies that the initial level of SWA (e.g., during the first one or two hours) increases as a function of the duration of prior wakefulness (e.g.,[9-11]). In the course of sleep, SWA decreases reflecting the recovery function of sleep.[9,12] It has recently been shown, that the sleep pressure build-up during wakefulness and its dissipation during sleep vary independently across individuals, thus, displaying distinct dynamics.[13] In addition to the higher initial level of SWA after ASD, there is also a faster dynamic of SWA build-up during the beginning of a sleep episode after ASD.[9,11] Furthermore, EEG recordings using a large number of electrodes revealed regional differences in the SWA increase after ASD, with frontal regions showing most pronounced effects.[14-16] Regional differences also exist in the dynamics of sleep pressure build-up across the cortex.[17,18] Thus, when estimating the dynamics of the sleep pressure build-up based on ASD data, not only differences between cortical areas but also between subjects were found.[17]

Some studies further investigated the changes in SWA during and following CSR. A less consistent picture emerges because the magnitudes of the SWA increase seemed to depend on the time-window in which SWA was assessed.[19-21] More precisely, increases in SWA during CSR were only evident when compared to SWA during an equivalent time window during baseline sleep (i.e., not to the whole baseline night).[19,21] Additionally, increases in SWA during recovery sleep following CSR have only been found for the first half of the sleep period (i.e., about first 4 hours), not for the second half.[20] Furthermore, the faster build-up of SWA was more pronounced during the first sleep cycle compared to later ones.[20]

It has been shown that between-subject differences in sleep pressure build-up rates, assessed in one central derivation, are stable across repeated exposure to ASD.[13] However, no study investigated up to date whether the magnitude of the sleep pressure increase, reflected by increased initial SWA, is related in the same individuals undergoing ASD and CSR. In other words, it is has not been shown whether the individuals responding with a relatively large increase in SWA after ASD also respond with a relatively large increase after CSR. Furthermore, it is unknown whether such an agreement would exist across all cortical areas. Our aim was therefore to assess whether an individual's homeostatic response to sleep loss is 1) preserved between ASD and CSR and 2) consistent across cortical areas and 3) related to classical behavioral markers of increased sleep pressure, i.e., vigilance impairments.

METHODS

Study Design

The study was conducted in the sleep laboratory at the Department of Neurology of the University Hospital Zurich and comprised an ASD condition of 40 hours of continuous wakefulness and a CSR condition consisting of 7 consecutive nights with time in bed restricted to five hours per night. Subjects underwent both conditions in a counter-balanced order and times in the protocol were adjusted to individual habitual bedtimes. Both conditions were separated by at least two weeks and were preceded by one week of regular sleep-wake rhythm with time in bed fixed to eight hours per night, which was

controlled by wrist-actigraphy[22] (on the non-dominant wrist; light sensor data included, ActiWatch, Respironics) and sleep diaries. The ASD was performed in the laboratory under constant supervision. The CSR was achieved by delaying the individual bedtime by two hours and advancing the wake-up time by one hour. The subjects spent the first four nights of CSR at home and the last three nights in the sleep laboratory. During the times at home, compliance to restricted time in bed was controlled by actigraphy, sleep diaries and phone calls. Here we compared baseline sleep ~~(assessed at the beginning of the protocol)~~ to recovery sleep following 40 hours of ASD and to sleep following seven nights of CSR. Bedtimes were kept constant during baseline and recovery nights and time in bed was fixed to eight hours. The baseline sleep assessments were performed in the sleep laboratory right before the first sleep manipulation (either the night before ASD or CSR) after subjects had adhered to a regular sleep-wake rhythm with bedtimes of eight hours per night for one week. The subjects arrived at the laboratory around two hours prior to their scheduled bed time. Vigilance was assessed every three hours, starting one hour after habitual wake-up time until three hours prior to habitual bedtime (5 assessments per condition in total), during the day following the baseline sleep assessment, after the night of ASD and after the seventh night of CSR.

The study was approved by the local ethics committee and all subjects gave written informed consent.

Subjects

Data presented in the current manuscript constitute a subpart of the complete data set, i.e., nine of the totally 14 subjects undergoing this study were included in the analysis, as no sleep recordings after completion of CSR were available in the other five subjects. The subjects were 18-26 years old (mean ± s.d.: 21.2 ± 2.4 years) and reported regular sleep durations of seven to eight hours per night (7.6 ± 0.4 hours). All of them were male, right-handed, in good general health, reported no regular medication intake, excessive caffeine consumption or drug or alcohol abuse, were non-smoking, did not work shifts, did not travel across more than two time zones for at least one month prior to study participation and reported no sleep complaints or excessive daytime sleepiness (according to the Pittsburgh Sleep Quality Index[23] and the Epworth Sleepiness Scale[24]). A screening night in the sleep

laboratory was performed to exclude any undiagnosed sleep disorders (e.g., sleep apnea or periodic leg movements), to ensure subjects had sufficiently high sleep efficiency (> 80%) and to let the subjects adapt to the laboratory environment and EEG equipment.

Subjects had to refrain from caffeine, alcohol and any medications starting three days prior to and throughout the ASD and CSR protocols. Furthermore, no food and drinks (except water) were allowed 30 minutes prior to any sleep or behavioral recordings. To avoid excessive sweating or heating, no extensive exercises or sauna were allowed on days with recordings.

Sleep EEG Recordings and Spectral Analysis

Because the increase in SWA after sleep loss has previously been reported to display regional differences,[14-16,25] sleep was recorded by high-density EEG nets consisting of 128 electrodes (Electrical Geodesics Inc. Sensor Net for long-term monitoring) including electrooculogram and electromyogram. The net was applied and adjusted to the vertex (Cz) right before bedtime and electrode impedances were kept below 50 kΩ. Sleep was recorded throughout the time in bed with a sampling rate of 500 Hz. Offline processing was conducted in Matlab (The Mathworks, Inc.). In accordance with previous studies,[26] the processing included data filtering (0.5 Hz high-pass, 40 Hz low-pass), down-sampling to 128 Hz, visual sleep stage scoring based on 20-second epochs according to standard criteria,[27] visual and semi-automatic rejection of artifactual epochs,[28] rejection of poor-quality channels (≤ 2 channels per recording) and exclusion of channels below the ears (to avoid artifacts induced by facial and neck muscles) and re-referencing of the data to the mean of all un-rejected channels. Throughout the manuscript, we refer to sleep stages according to the AASM Scoring Manual Version 2.0,~~.~~ (Ref) i.e., NREM sleep was subdivided into stages N1, N2 and N3.

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Sleep cycles were defined according to the criteria of Feinberg and Floyd.[29] In one subject the first sleep cycle was markedly prolonged and displayed two clear SWA peaks separated by a trough in one night (baseline) in comparison to other nights and cycles in this subject. Such a phenomenon has previously been described as a failure to visually detect REM sleep in the first sleep cycle.[30] Thus, according to previous studies the first NREM episode was defined to last only up to the trough of SWA

in this case (e.g.,[31,32]). This subject was not included in the calculation and comparison of REM sleep latencies.

SWA for all artifact-free N2 and N3 epochs was calculated in each electrode as the mean spectral power in the range of 1 – 4.5 Hz (Fast Fourier Transform routine, Hanning window, averages of five 4 second epochs). SWA of previously rejected channels due to bad quality were interpolated using a spherical interpolation,[33] resulting in SWA data of 109 channels in each subject and condition (without the electrodes below the ears). SWA was on the one hand averaged across the first hour of artifact-free N2 and N3 epochs (corresponding to 180 20-second epochs), and on the other hand over the first NREM episode. Furthermore, to assess SWA during the initial SWA build-up period, we averaged SWA over all N2 and N3 epochs up to the time point of maximal global SWA. The time point of maximal global SWA was determined based on 2-min intervals (mean SWA over 6 consecutive 20-second epochs averaged over all electrodes), i.e., the time point of maximal global SWA was defined as the 2-min interval with highest SWA (which was during the first sleep cycle in all subjects).

Increases in SWA were always calculated as percentage change to the corresponding baseline level.

Assessment of Vigilance

Vigilance was measured using the psychomotor vigilance task (PVT; PVT-192, Ambulatory Monitoring Inc.),[34] a sustained visual vigilance reaction time task. Lapses (i.e., count of reaction times > 500 ms) in the PVT have been shown to be sensitive to the condition of ASD and CSR.[35] Furthermore, a trait-like vulnerability for the increase in PVT lapses has been shown to persist across ASD and CSR.[8] We transformed the number of lapses (x) by the following formula ~~$\sqrt{x} + \sqrt{(x+1)}$~~ to approximate normal distribution of the data~~.~~[36]: $x_{trans} = \sqrt{x} + \sqrt{(x+1)}$. We than averaged the values across all five assessments per condition (baseline, ASD, CSR) in line with previous studies.[7,8,37] Increases in lapses were calculated as the difference between baseline values and values during ASD and CSR, respectively.

Statistics

All statistical tests and corresponding figures were realized in Matlab or R[38] (using different toolboxes and packages).[33,39-43] SWA between conditions and the difference in SWA increase after ASD and CSR were compared electrode-wise by paired-samples t-tests. Associations between SWA increases after ASD and CSR and the association of SWA increase and the increase in PVT lapses was assessed by Pearson's correlation coefficients. To control for multiple comparisons, we performed non-parametric statistical mapping (SnPM) with suprathreshold cluster testing[44] as previously applied in high-density EEG studies.[21,45,46] To assess the mean ± s.e.m across correlation coefficients in a significant cluster, Fisher's z-transform was applied to every correlation coefficient before averaging. The obtained averages were transformed back afterwards.

To exclude that the correlation between the increases in SWA after ASD and after CSR was mainly driven by the common baseline values, we additionally calculated partial correlations. When controlling for baseline SWA levels the partial correlation coefficients for the percentage increase in SWA after ASD and CSR were comparably high as in the zero-order Pearson correlation (data not shown). as were the partial correlation coefficients for absolute SWA after ASD and CSR. Furthermore, we performed a permutation analysis with SWA values of one sleep condition being permutated (20'000 permutation) before the ratios were built with the common baseline value. The real correlation coefficient was significantly higher ($P < 0.05$) than the ones observed in the permutations (data not shown). Thus, it seems unlikely that baseline levels of SWA ~~were unlikely to~~ have driven the correlation between the increases in SWA and only zero-order correlation coefficients are presented.

Kommentiert [BC1]: Plural?

We further checked, whether SWA in the chosen time-window displayed stable and robust inter-individual differences across all three conditions by calculating the intraclass correlation coefficient (ICC) as done in previous studies for all-night SWA (Tucker).

For the correlation between the SWA increase and the increase in PVT lapses we pooled the data obtained during ASD and CSR in order to increase statistical power and to assess the association across both conditions. To exclude that mainly differences between subjects drive any correlation (as every subject contributed two data points to the correlation), we further performed a mixed model analysis in which the random factor *subject* was included in a linear model predicting the increase in

PVT lapses by the increase in SWA. We tested whether including the random factor *subject* significantly increased the model fit - i.e., whether the random factor should be included in the model or not - by comparing the deviance of the models with a χ^2-Test. Of the 76 electrodes showing a significant association between SWA increase and increase in lapses, only 5 electrodes displayed a significant increase in model fit by including the random factor *subject*. The association between SWA increase and increase in lapses remained significant in all but 1 electrode when performing the mixed model analysis. Hence, Pearson's correlation coefficients are reported in the results, to stay consistent over all electrodes. Nevertheless, we would like to note that performing this analysis despite the lack of improved model fit in the majority of electrodes (102 out of 109), resulted in a very similar pattern of significant association between SWA increase and increase in PVT lapses (data not shown).

Additionally, to exclude that mere level differences between ASD and CSR would drive any correlation, we assessed the increase in adjusted explained variance when including the factor *condition* (ASD vs. CSR) as a second predictor for the increase in PVT lapses predicted by SWA increase in a linear model by the Akaike information criterion (AIC) and the Bayesian information criterion (BIC). Including the factor *condition* did not improve the model fit in any of the electrodes displaying a significant association between SWA increase and increase in lapses~~. Furthermore, the effect of the factor *condition* was not significant in any electrode when included anyway as a second predictor~~ (data not shown).

RESULTS

As the increase in SWA after ASD and CSR was put in relation to SWA during baseline, we carefully checked the baseline nights for any indication of low sleep quality. However, all subjects displayed well-defined sleep-cycles across the night with SWA values consistently being highest during the first sleep cycle, and all displayed a normal distribution of sleep stages during the night (Table 1). Furthermore, sleep stage distribution during the first sleep cycle did neither display any indication of frag-

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mented sleep (cf. Table 2), with low values of wake after sleep onset (WASO) and sleep stage N1 duration in all subjects (range WASO: 0 – 2.3 min; stage N1: 0 – 4.3 min) and high values of sleep stage N3 duration (range: 40.0 – 68.3 min).

Increased sleep efficiency and duration of deep sleep on the one hand and decreased sleep latency and shorter duration of lighter sleep stages (N1 and N2) on the other hand were found after ASD as expected due to the elevated sleep pressure. The changes in the variables after the CSR condition were similar but smaller in their extent (Table 1). REM sleep latency was decreased after ASD and CSR, while REM sleep duration only increased significantly after CSR (Table 1). Compared to both baseline and ASD, the first NREM sleep episode was markedly shorter after CSR (Table 2). Within this first NREM episode N1 and N2 duration were decreased after ASD and CSR and N3 duration was decreased after CSR only (Table 2), probably due to the shortened duration of the first NREM episode after CSR. Sleep efficiency was high in all three nights (Table 1), indicating that ~~sleep was not disturbed by~~ wearing high-density EEG nets did not ~~lead to low~~impair sleep quality.

Sleep loss is known to increase SWA especially during the initial part of sleep.[9,47] Variable time windows can be used to investigate this period. In a first step we chose a time window assessing the same number of epochs in every subject, i.e., the first hour of artifact-free N2 and N3 epochs. When using this time window, SWA topographies revealed a typical spatial pattern with maximal values over frontal regions in all three conditions (baseline, after ASD and after CSR; data not shown). We then contrasted the prolonged wakefulness conditions (ASD and CSR) to the baseline. Compared to baseline, SWA values during the first hour of NREM sleep were significantly increased in all electrodes after ASD (Figure 1A; mean increase over all electrodes ± s.e.m: +42.4 ± 6.3 %, cluster size: $P < 0.01$, SnPM suprathreshold cluster testing). In contrast, there was no significant increase in any electrode found after CSR (Figure 1A; mean increase over all electrodes: +2.5 ± 4.1%). This result, however, might be biased due to significantly reduced duration of the first NREM sleep episode after CSR (cf. Table 2): the first NREM episode was on average shorter than one hour after CSR whereas it was longer than one hour at baseline and after ASD. Individual data analyses revealed that indeed SWA of the first hour of N2 and N3 included exclusively epochs from the first NREM episode in 8 out of 9

subjects at baseline, but only in 2 out of 9 subjects after CSR. Hence, in 6 subjects the SWA values included an additional phase of SWA build-up during the second NREM episode after CSR but not at baseline.

Facing these differences in NREM episode duration, we next assessed SWA during the entire first NREM episode only. Indeed, it has been previously noted that a sleep cycle constitutes a physiological meaningful time range to assess SWA,[47,48] as it takes the structure of sleep into account. Following ASD, SWA during the first NREM episode was again increased in all electrodes compared to baseline (Figure 1B; mean increase over all electrodes: +46.0 ± 5.5 %, cluster size: $P < 0.01$, SnPM suprathreshold cluster testing) but also after CSR in a cluster of 20 electrodes over left centro-parietal and temporal regions (Figure 1B; mean increase in cluster electrodes: +18.5 ± 4.2 %, cluster size: $P < 0.05$, SnPM suprathreshold cluster testing; mean increase over all electrodes: +15.3 ± 4.1 %).

Sleep loss strongly affects the initial build-up of SWA, i.e., SWA not only reaches higher levels but also increases faster, reflecting the increase in sleep pressure during preceding prolonged wakefulness.[20,47,49] According to the two-process model of sleep regulation, the build-up of sleep pressure is reflected by the asymptotic level SWA reaches within a sleep cycle. In contrast, the decrease in SWA during the course of sleep reflects the dissipation of sleep pressure.[50] To account for these SWA dynamics, we assessed in a next step SWA from the onset of sleep up to the maximal level reached during the first cycle in every condition and for every individual separately (see methods for details). With this procedure we aimed at maximally separating the two aspects SWA levels are reflecting, i.e., 1) the accumulated sleep pressure during preceding wakefulness reflected in the initial levels and 2) the dissipation of sleep pressure reflected in the decreasing levels across sleep. Comparing SWA during this initial SWA build-up period revealed again a similar picture when comparing ASD to baseline, with all electrodes showing a significant and even more pronounced increase in SWA (Figure 1C, mean increase over all electrodes: +60.2 ± 8.7 %, cluster size: $P < 0.01$, SnPM suprathreshold cluster testing). After CSR, SWA during this time period was significantly increased in two large clusters of electrodes, i.e., 32 electrodes over fronto-cental regions and 26 electrodes over occipito-temporal regions (Figure 1C, mean increase over fronto-central cluster: +25.9 ± 9.5 %; over occipito-temporal

cluster: +23.3 ± 8.3%, both cluster sizes: P < 0.05, SnPM suprathreshold cluster testing). As this measure of SWA increase displayed the spatial pattern typically reported in previous sleep loss studies (e.g.,[15]) and showed a notable increase in both conditions of sleep loss, we continued our analysis with the increase in SWA during the initial build-up period. Notably, we observed an ICC of 0.73 for SWA averaged over all electrodes during the initial build-up period. This indicates substantially stable and robust inter-individual differences (Ref) in SWA during this time-window across all three conditions, which has been previously shown for all-night SWA across baseline and ASD recovery nights (Tucker).

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Next, we directly compared the two sleep loss conditions and found that the increase in SWA during the initial build-up period was more pronounced after ASD than after CSR in all electrodes (Figure 2A, average difference of increase after ASD compared to after CSR over all electrodes: +38.48 ± 4.6%, cluster size: P < 0.01, SnPM suprathreshold cluster testing). This difference fits well to the observed changes in sleep architecture also indicating a larger increase in the level of sleep pressure after ASD than CSR (cf. Table 1). To assess whether subjects showing a relatively large increase in one condition did so also in the other condition and vice versa, we correlated the increase after ASD and CSR. We found that the increase in one condition was significantly correlated with the increase in the other condition in 90 electrodes forming a widespread pattern of positive associations (Figure 2B and 2C, mean *r* over these electrodes: 0.83 ± 0.02, cluster size: P < 0.05, SnPM suprathreshold cluster testing). Hence, while ASD introduced a stronger increase in sleep pressure compared to CSR, subjects responding to ASD with a large response did so in the CSR condition too. Please note, that this correlation was not merely driven by differences in baseline SWA, as controlling for the baseline level did not change the extent of association (see methods for details).

Finally, we assessed whether the increase in SWA during the initial build-up period relates to the neurobehavioral impairments that occurred during preceding wakefulness. To do so we correlated the increase in SWA during the initial build-up period after both sleep loss conditions with the increase in PVT lapses and found a rather global, widespread positive association in 76 electrodes between these two measures (Figure 3, mean *r* over these electrodes: 0.62 ± 0.02, cluster size: P < 0.05,

SnPM suprathreshold cluster testing). The pattern of the association was similar for both sleep loss conditions separately (data not shown) and was not driven by the inclusion of multiple (i.e., 2) data points per subject or by mere level differences between conditions, as controlling for these factors did not significantly change the association (see methods for details).

DISCUSSION

The individual homeostatic increase in sleep pressure, as reflected by the increase in SWA, of two sleep loss conditions was related in the majority of electrodes all over the scalp. Previously it has been shown that SWA levels per se and the SWA topography show trait-like characteristics across baseline conditions and ASD.[14,51] Also parameter estimations quantifying the dynamics of sleep pressure build-up have been shown to be trait-like across repeated ASD in the same individuals.[13] Our results add to these findings indicating that also the change in SWA induced by homeostatic challenges is preserved within an individual across different conditions of sleep loss.

Interestingly, it has been shown that an individual with relatively large neurobehavioral impairments after ASD does so also after CSR.[8] Thus, we assessed the relationship with PVT lapses. The positive relationship between the SWA increase and the increase in PVT lapses was rather widespread but varied in its extent across cortical areas. We acknowledge that a lack of significant correlations in some areas might be the result of low power considering the small sample size. However, the lack of a strong association in frontal electrodes seems surprising at first glance as the frontal cortex has been shown to respond particularly strong to sleep loss.[14-16,25] This unexpected finding could potentially be explained by compensatory mechanisms as for example a higher activation following sleep loss in some frontal areas that has been linked to less drowsiness.[52] Since SWA has been shown to locally increase in a use-dependent manner,[53-56] less vulnerable subjects showing compensation-related higher activity in frontal areas could be expected to display a further, potentially un-proportional increase in frontal SWA. As a result, we would not expect a linear but a more complex relationship between SWA increase and behavioral impairments in areas being recruited successfully in a compensatory manner.

Up to date, it is still largely unclear which factors exactly contribute to individual differences in the vulnerability to sleep loss induced cognitive impairments.[57] It has been suggested that impairments result from repetitive use of distinct neuronal groups involved in a given cognitive process which as a result fail to function due to emerging local restoration need. Furthermore, individuals are thought to differ in the extent they are vulnerable to such use-dependent effects in specific neuronal groups.[58,59] One

could speculate that the local extent of increased SWA at the beginning of sleep reflects such a vulnerability. Moreover, also local use-dependent increases of SWA on top of the global increase were observed after prolonged wakefulness.[53,55] The rather wide-spread than local association we found between the increase in SWA and the increase in PVT lapses fits to the notion that not only one specific cortical area is thought to be responsible for lapsing.[60] Nevertheless, performance in other cognitive tasks might depend differently on distinct brain areas. Estimations of sleep pressure build-up rates based on ASD data display distinct spatial patterns and vary significantly between individuals.[17] This further indicates that such spatial differences might be an underlying mechanism of differential individual vulnerabilities to sleep loss impairments across different cognitive processes.[57,61-63] Hence, it seems reasonable that the relationship between increased SWA and impairments in more specific cognitive processes would display spatially more restricted associations which could be assessed by high-density EEG. However, this remains speculative and requests further investigation.

Our analysis revealed that the time window in which SWA is assessed might be important when investigating the effects of CSR. The observed changes in sleep structure, i.e., changed duration of the first NREM episode and duration of N3 in the first NREM episode, might lead to a bias in SWA values between different conditions when a fixed time window is analyzed. Assessing and dealing with such changes in dynamics seems especially important in the condition of CSR. One reason for this could be the lower extent of sleep pressure increase after CSR, given the duration and extent with which it was realized in this study. A lower increase might be more sensitive to biases. Another reason for the stronger bias in CSR outcome measures could be the observed increase in REM sleep pressure as reflected by the significant increase in REM sleep duration and the decrease in REM sleep latency, which has previously been reported to occur after CSR.[19-21,53,64] The increased REM sleep pressure after CSR could interact with the increased NREM sleep pressure, causing the first NREM sleep episode to be shorter, similar to the observation of sleep onset REM in individuals with chronically insufficient sleep durations.[65] Furthermore, simulation studies have shown previously that differences in REM sleep latencies consequently result in differences in SWA values of the first NREM episode.[66] Thus, we believe that the most unbiased measure in our case was SWA during the initial build-up pe-

riod, as it is not primarily influenced by shorter NREM episode durations per se. This was also evident, when comparing the number of epochs included in the analysis, which was significantly different between conditions when the whole first NREM episode was analyzed, but not when analyzing SWA during the initial build-up period up to the maximal 2-min epoch (cf. Table 2). Additionally, we have chosen this time-window, as the initial level of SWA is thought to reflect the accumulated sleep pressure during preceding wakefulness on the one hand[9,10] and is also thought to be functionally involved in the dissipation of sleep pressure across the night on the other hand.[67] The processes of sleep pressure build-up during wakefulness and of sleep pressure dissipation during sleep have been shown to be independent, i.e., not related within an individual.[13] Hence, larger time windows, not taking into account the dynamics of SWA and therefore also including times of declining SWA, as it occurs within and across consecutive sleep cycles,[9,20,47] might represent a mixture of these processes and result in SWA values not adequately reflecting the level of increased sleep pressure resulting from preceding wakefulness.

A major limitation in our study is certainly the small number of subjects, which might have caused some power issues in statistical analysis. While we carefully ~~checked.~~confirmed that baseline SWA levels were not compromised by low sleep quality, it would be favorable to assess baseline SWA levels as the average across multiple baseline nights in future studies ~~in order~~ to achieve a stable and robust baseline to refer to. Furthermore, we cannot exclude that the findings are restricted to young, healthy male subjects with habitual sleep times of 7-8 hours. Thus, the findings should be replicated in a larger and more heterogeneous population. Because we only assessed SWA after the completion of CSR, we cannot make any assumptions about the time course or dose-response of the SWA increase during CSR. As our study was not designed to address this aspect, future studies, including the assessment of the SWA increase during the whole course of CSR could therefore provide additional information on that issue.

Conclusion

We show here, that the individual extent in homeostatic response as measured by the SWA increase is related across chronic and acute sleep loss. This relationship was not limited to certain brain areas but evident in a widespread pattern all over the cortex. Furthermore, the SWA increase was associated with impairments in vigilance over both conditions and might therefore provide a physiological marker for individual differences in performance impairments after sleep loss. This might be an important step towards a better understanding of mechanisms underlying the individual vulnerability to sleep-loss induced neurobehavioral impairments.

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CONFLICT OF INTEREST

The authors declare no competing financial interests.

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